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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/288,837 | 04/08/99 | MACDONALD G | 5470-238 |

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| EXAMINER | |
|---|---|
| BRUMBACK, B | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | 10 |

**DATE MAILED:** 10/18/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/288,837 | MacDonald et al. |
| **Examiner** | **Group Art Unit** |
| Brenda Brumback | 1642 |

☒ Responsive to communication(s) filed on *Aug 9, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-8 and 11-84* is/are pending in the application.

Of the above, claim(s) *17-83* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8, 11-16, and 84* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 & 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Election/Restriction*

1. Applicant's election with traverse of Group I, claims 1-16 and 84 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to simultaneously examine the claims of Groups I-III. This is not found persuasive because due to their different classification and/or their recognized divergent subject matter, the searches for Groups II and III are not required for Group I; thus, simultaneous examination of all three groups would constitute an undue burden.

The requirement is still deemed proper and is therefore made FINAL.

2. The Preliminary Amendment filed 08/09/2000 (Paper # 9) is acknowledged. Claims 9 and 10 were canceled. Claims 1-5, 11, 13, 16 were amended. New claim 84 was added. Pending claims are 1-8 and 11-84. Claims 17-83 are withdrawn from consideration as directed to a nonelected invention. Claims under examination are 1-8, 11-16, and 84.

### *Information Disclosure Statement*

3. The Information Disclosure Statements filed 08/18/1999 and 03/06/2000 (Papers # 4 and 5 respectively) are acknowledged. Signed copies are attached hereto. **Please Note**: Reference #1 in Paper #4 was not considered as the enclosed copy of the reference was incomplete. For

consideration of this reference, a complete copy including all of the page numbers and the author's name must be submitted.

### *Claim Objections*

4. Claims 1 and 84 are objected to because of the following informality. The adjective "immunogenic" in line 2 or each of the claims should be amended to the adverb -- immunogenically -- in order to correct the grammar, since the term modifies an adjective . Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

5. Claims 1-8, 11-15, and 84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 84 are drawn to a composition comprising alphavirus particles comprising heterologous nucleotide sequences. Because of the double use of the term "comprising" it is unclear what is encompassed within the claimed composition. For purposes of examination, the claims have been interpreted as drawn to a composition consisting essentially of alphavirus particles comprising a heterologous nucleotide sequence.

Claim 6 recites a composition comprising infectious Venezuelan Equine Encephalitis Virus (VEEV) particles comprising one or more attenuating mutations selected from codons at E2

amino acid (AA) position 76, codons at E2 AA position 120, etc. The claims are indefinite as there is neither a VEEV sequence listing in the disclosure delineating the reference VEEV AA sequence, nor is there a reference incorporated into the disclosure providing the reference sequence. Absent a teaching of the reference sequence which is the basis for the attenuating mutations, the claims are indefinite.

Claim 13 is indefinite for recitation of an improper Markush group. The claim recites at least one nucleotide sequence selected from a Markush group reciting epitopes. An epitope is defined as an antigenic determinant specific for an antibody, not as a nucleotide. For this reason, the Markush group is improper and the claim is indefinite.

Claim 13 is also indefinite for recitation of an antigen selected from T and B cell epitopes. An epitope is defined as an antigenic determinant specific for an antibody. Absent some teaching in the disclosure as to what antigenic determinants are encompassed within the recited epitopes, the metes and bounds of the claimed invention cannot be determined and the claim is indefinite.

### *Claim Rejections - 35 USC § 102*

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

a. Claims 1-3, 11-15, and 84 are rejected under 35 U.S.C. 102(a) as being anticipated by Song et al. (*WO 97/24447, of record in paper # 5*).

The claimed invention is drawn to a composition comprising alphavirus replicon particles, specifically VEEV particles, in an immunogenically effective amount, wherein the particles comprise one or more heterologous nucleotide sequences encoding either a native cancer cell antigen or an artificial cancer antigen (an infectious disease antigen, for example) that is not normally expressed by a cancer cell. Dependent claims recite the antigen as selected from an influenza hemagglutinin (HA) antigen, T cell and B cell epitopes, and a cell-surface protein.

Song et al. teach pharmaceutical compositions comprising alphavirus replicon particles for gene delivery *in vivo* or *in vitro*, wherein the alphavirus is VEEV and comprises one or more heterologous nucleotide sequences encoding a native cancer-associated antigen, an altered cellular component, or an antigen from a foreign organism, such as influenza virus. Song et al. teach a cell-mediated immune response as a result of immunization with the particles (see the abstract; page 2, lines 5-30; page 4, lines 1-7, 16-18, and 27-29; page 5, lines 1-2; page 6, lines 3-4; page 11, lines 11-19; page 17, lines 3-10; and page 19, lines 24-29).

b. Claims 1-3, 7, 11-15, and 84 are rejected under 35 U.S.C. 102(b) as being anticipated by Dubensky et al. (WO 95/07994).

The claimed invention is drawn to a composition comprising alphavirus replicon particles (VEEV) in an immunogenically effective amount, wherein the alphavirus particles comprise one

or more heterologous nucleotide sequences encoding either a native cancer cell antigen or an artificial cancer antigen that is not normally expressed by a cancer cell. Dependent claims recite the antigen as selected from an influenza hemagglutinin antigen (HA) and a cell-surface protein, and also recite that each of the heterologous nucleotide sequences is operably associated with a promotor.

Dubensky et all teach recombinant alphavirus vectors (VEEV) (see page 3, lines 8-10, and page 9, lines 10-12) comprising one or more heterologous sequences (page 1, lines 6-8; page 4, lines 15-16) operably associated with a promotor (page 3, line 36, through page 4, line 5) selected form influenza virus antigen (page 4, lines 24-27), native cancer antigens, and artificial cellular cancer antigens (page 6, lines 17-27, and page 27, line 17, through page 33, line 30).

c. Claims 1-8, 11-13, and 15 rejected under U.S.C. 102(b) as being anticipated by Johnston et al. (WO 95/32733; of record in Paper # 5).

The claimed invention is drawn to a composition comprising an immunogenically effective amount of infectious alphavirus particles, or specifically VEEV particles, in a pharmaceutically acceptable carrier, wherein the VEEV particles comprise one or more heterologous nucleotide sequences encoding an artificial cancer antigen that is not normally expressed by a cancer cell. Dependent claims recite the VEEV particles as comprising one or more attenuating mutations selected from codons at E2 AA positions 76, 120, and 209; codons at E1 AA positions 272, 81, and 253; and deletion of E3 AA at positions 56-59. Dependent claims also recite the

heterologous nucleotide sequence as an infectious disease antigen or specifically as an influenza HA antigen or as a T-cell or B-cell epitope, the antigen operably associated with the alphavirus 26S subgenomic promotor.

Johnston et al. teach a composition comprising an immunogenic amount of VEEV containing a heterologous RNA segment operably associated with the VEEV 26S subgenomic promotor (see the abstract). Johnston teach that the constructs produce protective B and T-cell mediated immunity (see page 1, lines 20-22). Johnston et al. teach the VEEV particles as comprising one or more attenuating mutations selected from codons at E2 AA position 76, 120, and 209; codons at E1 AA position 272, 81, and 253; and inactivation of E3 AA 56-59 (see page 5, lines 26-32 and page 3, lines 3-23). Johnston et al. teach the heterologous nucleic acid as encoding an influenza virus hemagglutinin surface protein, among others (see page 6, lines 30-36). Because the influenza HA antigen is an antigen which is not normally expressed by a cancer cell, Johnston et al. anticipate the claimed invention.

## *Claim Rejections - 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 11-16 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. in view of Falo Jr. et al. (U.S. Patent 5,951,975, of record in paper #4).

The claimed invention has been interpreted as drawn to a composition comprising an immunogenically effective amount of a composition consisting essentially of infectious alphavirus particles and specifically VEEV particles in a pharmaceutically acceptable carrier, wherein the VEEV particles comprise one or more heterologous nucleotide sequences encoding either a native cancer cell antigen or an artificial cancer antigen that is not normally expressed by a cancer cell. Dependent claims recite the VEEV particles as comprising one or more attenuating mutations selected from codons at E2 AA positions 76, 120, and 209; codons at E1 AA positions 272, 81, and 253; and deletion of E3 AA at positions 56-59. Dependent claims also recite the heterologous nucleotide sequence as an infectious disease antigen or specifically as an influenza HA antigen, a cell surface protein, or a T-cell or B-cell epitope, the antigen operably associated with the alphavirus 26S subgenomic promotor. Claim 16 is drawn to a kit comprising components for determining pre-existing immunity to one or more antigens in a subject afflicted with cancer and one or more vectors comprising a heterologous nucleotide sequence encoding the antigens.

As described above, Johnston teaches a composition comprising an immunogenic amount of a VEEV vaccine vector comprising a heterologous RNA segment operably associated with the alphavirus 26S subgenomic promotor. Johnston et al. teach the VEEV particles as comprising one or more attenuating mutations and teach the heterologous nucleic acid as encoding an

influenza virus HA surface protein, among others. Johnston teaches that the constructs elicit protective B and T-cell mediated immunity against the heterologous antigen (see page 1, line 15, through page 2, line 6 and page 2, line 33, through page 3, line 2). Johnston differs from the claimed invention in that he does not teach the heterologous nucleic acid as encoding a native cancer antigen and does not teach the vaccine composition as targeted to a cancer.

Falo teaches that, although certain tumor antigens are known, it not feasible to identify relevant tumor antigens for each individual patient in order to stimulate antigen specific CTL production and destruction of neoplastic cells (see column 3, lines 37-45). Falo teaches prophylactic and therapeutic anti-tumor immunization based on cross-priming a mammalian host to natural MHC class I restricted tumor antigens with an artificial tumor antigen (see the abstract). Falo teaches priming a mammalian host with an artificial antigen such as an influenza virus antigen or a tumor antigen, resecting the tumor from the host and culturing the cells *in vitro*, engineering the cultured cells to present the artificial antigen on the cell surface, inactivating the engineered cells, and reintroducing the cells back into the host. Falo teaches that once introduced back into the host, the tumor cells focus the immune response against host tumor cells in a manner sufficient to stimulate CTL-mediated immunity to multiple, additional undefined natural tumor antigens present on unmodified host tumor cells (see column 3, lines 38-65, and column 4, line 22, through column 5, line 15).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have primed a cancer patient's immune system with an artificial cancer

antigen, such as an influenza HA antigen or a tumor antigen as is taught by Falo, or alternatively to have selected an antigen to which a cancer patient's immune system is already primed through previous vaccination as is suggested by Falo, and then to have used the VEEV vector taught by Johnston as an efficient means for introducing the artificial cancer antigen into a portion of the tumor cells of the patient, in order to stimulate a protective CTL-mediated immunity to multiple, additional undefined natural tumor antigens present on unmodified host tumor cells without having to isolate and characterize patient specific antigens.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Davis et al., Vaccines 95: Mol. Approaches Control Infect. Dis., (Annu.Meet.), 12th EDITOR: Chanock, Robert M (Ed), DATE: 1995 PAGES: 387-91 teach compositions consisting of VEEV particles comprising heterologous nucleotide sequences encoding the influenza HA antigen or HIV-1 *gag* and *env* antigens.

Davis et al., Journal of Virology, 70(6):3781-3787, 1996, teach VEEV particles configured for *in vivo* expression of heterologous immunogens and specifically for expression of influenza HA antigen.

Pushko et al., Virology 239:389-401, 1997 (of record in Paper # 5) teach a replicon vaccine vector system consisting of VEEV particles wherein the structural proteins are replaced with the influenza HA or the Lassa virus nucleocapsid gene.

***Conclusion***

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
October 10, 2000

Brenda Brumback
Brenda Brumback,
Patent Examiner